UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,143	08/16/2005	Eric E Schadt	ROSA134261	6414

26389 7590 12/30/2010

CHRISTENSEN, O'CONNOR, JOHNSON, KINDNESS, PLLC
1420 FIFTH AVENUE
SUITE 2800
SEATTLE, WA 98101-2347

EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
12/30/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

efiling@cojk.com

Office Action Summary	Application No.	Applicant(s)	
	10/523,143	SCHADT ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,23-25,28-30,33,35-37,40-50,52-54,107,252,253,258,262,273 and 274* is/are rejected.

7)☒ Claim(s) *252 and 259-261* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-21,23-25,28-30,33,35-37,40-50,52-54,107,252,253,258-262,273 and 274.

DETAILED ACTION

Status of the Claims

1. Claims 1-21, 23-25, 28-30, 33, 35-37, 40-50, 52-54, 107, 252, 253, 258-262, 273, and 274 are pending.

2. Claim 252 and 259-261 are objected to.

3. Claims 1-21, 23-25, 28-30, 33, 35-37, 40-50, 52-54, 107, 252, 253, 258, 262, 273, and 274 are rejected.

Continued Examination Under 37 CFR 1.114

4. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12 November 2010 has been entered.

Claim Objections

5. Claim 252 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 252 requires that the an association between gene G and clinical trait T is tested by determining genetic linkage between the eQTL and the cQTL, which is performed in step (C) of claim 1 from which claim 252 depends.

Claim Rejections - 35 USC § 112

6. The rejection of claims 259-261 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention in the Office action mailed 12 May 2010 is withdrawn in view of the amendment to the claims received 12 November 2010.

Claim Rejections - 35 USC § 102

7. The rejection of claims 1, 2, 5-11, 42-44, 49, 50, 52, 53, 252, and 258 under 35 U.S.C. 102(b) as being anticipated by Aitman et al. in the Office action mailed 12 May 2010 is withdrawn in view of the amendment to the claims received 12 November 2010.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-21, 23-25, 28-30, 33, 35-37, 40, 50, 52, 53, 252, 273, and 274 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aitman et al. '99 (cited as reference C01 in the Information Disclosure Statement filed 06 March 2006, Nature Genetics Vol. 21, pages 76-83 (1999)) in view of Aitman et al. '97 (Nature Genetics, Vol. 16, pages 197-201 (1997).

The claims are drawn to a method of measuring an expression quantitative trait locus (eQTL), a clinical quantitative trait locus (cQTL), and determining whether the gene assayed in the determination of the eQTL and the clinical trait are associated by determining if the eQTL and cQTL map to the same locus. The eQTL is determined by iteratively scanning positions in the chromosome. In some embodiments the association is confirmed if the eQTL maps to the gene that is the trait, i.e. the eQTL is a cis eQTL as discussed on page 95 of the specification. In some embodiments the eQTL and the assayed gene are within 1centiMorgan (cM) of each other, the eQTL and cQTL are the same QTL, the analysis uses genetic maps reflecting the genotype of an individual, the analysis uses restriction fragment length polymorphisms, the expression value is normalized, the normalization is done by either a normalization gene set, a ratio median correction, or a background correction, the expression value is determined by analysis of RNA abundance using a hybridization assay to an array of probes, the analysis uses pedigree data and F2 populations, the eQTL and cQTL are colocalized within 6 centimorgans (cM), genetic linkage is observed between the eQTL and the cQTL, and the eQTL and the cQTL are shown to be a common QTL and are not merely in linkage disequilibrium (i.e., closely linked). In some embodiments the eQTL is determined by scanning positions in all chromosomes. In some

embodiments the scanning is done in increments less than 2.5 cM. In some embodiments the eQTL has a statistical logarithm of the odds (LOD) score that is greater than 5.0. In some embodiments the cQTL is determined by iteratively scanning positions in the genome. In some embodiments the scanning is done in increments less than 2.5 cM. In some embodiments the cQTL has a LOD score greater than 5.0. In some embodiments the eQTL and the cQTL are within 6 cM of each other.

Aitman et al. '99 shows in the abstract a method of genetically analyzing diabetes by correlating a cQTL of quantitative traits of diabetes (insulin-mediated glucose uptake and catecholamine-mediated lipolysis) with an eQTL (Cd36) that correlates with the same traits. Aitman et al. '99 used spontaneously hypertensive rat (SHR) animals to map both eQTL and cQTL. Aitman et al. '99 employed 401 F2 crosses to map insulin-mediated glucose uptake and catecholamine-mediated lipolysis to a region near the microsatellite marker D4Bro1 in the second column of page 76 to the first column of page 77 with a LOD score of 8.8, which is a determination of a cQTL. In the first column of page 79, Aitman et al. '99 employs F2 crossed rats to refine the mapping of insulin-mediated glucose uptake and catecholamine-mediated lipolysis to Cd36. Aitman et al. '99 shows in figure 2 and the discussion on pages 77-78 that analysis of expression level microarrays determined that expression of Cd36 correlates with SHR animals relative to SHR.4 (a congenic strain differing only in the relevant region of chromosome 4) and BN control animals. Polymerase chain reaction of chromosomal fragments was used to map Cd36 to a region near the D4Bro1 site in figures 3 and page 78 using radiation hybrids to a precision of about 1cM with a LOD of 5.1 to 9.6 for the intervals measured. The mapping used a plurality of rat/hamster radiation hybrid cell lines to test a plurality of chromosomal locations for

linkage to Cd36. Aitman et al. '99 then refined the mapping of Cd36 by use of linkage analysis on page 78 and figure 7 by testing linkage to chromosomal DNA of three rat strains. Pages 78-80 and figures 4, 6, and that rat strains SHR and control strains differ by mutations, duplications, and deletions in the Cd36 gene and that CD36 mRNA of SHR rats do not contain the CD36 exon 6. Aitman et al. shows in the legend to figure 2 and the methods section on page 82 that the sample applied to the microarray was made from mRNA. Aitman et al. '99 shows on page 82 that the microarray comprises control probes for housekeeping genes, and synthetic, yeast, and human probes that would not be expected to hybridize the rat cDNA samples. Two differently fluorophore labeled samples from different rat strains were simultaneously applied to the microarray, and the ratios of hybridization were determined for each probe on the microarray. Aitman et al. '99 used the computer program MAPMAKER QTL as noted in the first column of page 79.

Aitman et al. '99 does not discuss how the raw data of the microarray was processed to give the final expression ratios reported on page77. Aitman et al. '99 does not show explicitly that chromosomes were scanned to map either expression or clinical quantitative trait loci.

Aitman et al. '97 is referenced in Aitman et al. '99 on the second column of page 76-the first column of page 77 as showing that a gene on rat chromosome 4 has pleiotropic influences (at least insulin and catecholamine action) on fatty acid metabolism. Aitman et al. '97 performs a genome screen for loci linked to insulin and catecholamine action. In the Methods section in the second column of page 200, Aitman et al. '97 shows that 96 microsatellites were used to give more than 90% coverage of the rat genome as a sweep of 20 cM, with a minimum of 64% coverage on each autosome. Figure 1 shows linkage analysis for chromosomes 4 and 12, with

data points of crosses mapped by the satellite markers plotted against LOD scores. Figure 1a shows 45 data points for crosses approximately 2 cM apart. Aitman et al. '97 shows in the abstract and figure 1 a quantitative trait locus on chromosome 4 for defective insulin and catecholamine action. This locus is equivalent to a clinical QTL because it correlates a quantitative clinical trait with a genetic locus. Aitman et al. '97 used the computer program MAPMAKER QTL, as noted in the legend of figure 1 and the Methods section on page 200.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to scan chromosomes of an animal as part of a process of mapping a clinical quantitative trait locus because Aitman et al. '99 shows use of many crosses of animals to map a QTL and Aitman et al. '97 shows earlier experiments of the same laboratory in which crosses and satellite markers were used to scan more than 90% of the rat genome to map a QTL. It would have been further obvious to scan chromosomes of an animal to map an expression QTL because any quantitative trait could be used to map a locus by the method of Aitman et al. '97 and Aitman et al. '99 shows the importance of mapping an expression QTL. It would have been further obvious to map an expression QTL by scanning chromosomes because the expression QTL identified by Aitman et al. '99 was initially localized by the chromosome scanning procedure of Aitman et al. '97. It would have been further obvious to process the raw data of the microarray of Aitman et al. '99 by subtracting background hybridization levels by use of the non-homologous probe signal levels included in the microarray as controls, and it would be further obvious to convert the levels of each measured fluorophore for each probe as a ratio of signals rather than two raw signals because Aitman et al. '99 is interested in determining the relative levels of

expression of every measured gene in the two compared strains, as reported on page 77 of Aitman et al. '99.

10. Claims 1 and 41-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aitman et al. '99 in view of Aitman et al. '97 as applied to claims 1-21, 23-25, 28-30, 33, 35-37, 40, 50, 52, 53, 252, 273, and 274 above, and further in view of Dominiczak et al. (Hypertension Vol. 35 (part 2), pages 164-172 (2000)).

The claims are drawn to a method of measuring an expression quantitative trait locus (eQTL), a clinical quantitative trait locus (cQTL), and determining whether the gene assayed in the determination of the eQTL and the clinical trait are associated by determining if the eQTL and cQTL map to the same locus. In some embodiments the individual is a human. In some embodiments the clinical trait is a complex trait, the trait exhibits incomplete penetrance, the clinical trait is the effect of a mutation in a plurality of genes, the complex has a high frequency of disease causing alleles, the trait does not exhibit Mendelian inheritance, or the trait is hypertension.

Aitman et al. '99 in view of Aitman et al. '97 as applied to claims 1-21, 23-25, 28-30, 33, 35-37, 40, 50, 52, 53, 252, 273, and 274 above does not show an eQTL that maps to a plurality of positions in a genome. Aitman et al. '99 shows incomplete penetrance of a QTL in figure 1 and the first column of page 77. Aitman et al. '99 in view of Aitman et al. '97 as applied to claims 1-21, 23-25, 28-30, 33, 35-37, 40, 50, 52, 53, 252, 273, and 274 above does not show analysis of a human QTL (although Aitman et al. '99 notes on page 76 that human type 2 diabetes has similarities to the rat models studied in Aitman et al. '99), or analysis of a trait

affected by a plurality of mutations in different genes, or a high frequency of disease causing alleles of a trait, or a trait that is hypertension.

Dominiczak et al. reviews the genetics of hypertension. Dominiczak et al. shows on the first column of page 165 that human genes have been identified that contribute to hypertension (a quantitative trait) with a LOD score of greater than 2. Table 1 shows rat loci and alleles that confer hypertension in strains that contain the allele. The alleles are on different chromosomes, and contribute to hypertension with LOD scores ranging from 3.0 to 16.6. Dominiczak et al. notes the work of Aitman et al. '99 (as reference 44) on page 167 as being an important advance in genetic analysis of disease traits. Dominiczak et al. shows on pages 167 through 169 the use of congenic strains to map a QTL.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the analysis of Aitman et al. '99 in view of Aitman et al. '97 as applied to claims 1-21, 23-25, 28-30, 33, 35-37, 40, 50, 52, 53, 252, 273, and 274 above by analyzing human QTL markers, and to extend the analysis to a plurality of QTL markers with limited penetrance because Dominiczak et al. shows that hypertension is caused by a plurality of limited penetrance alleles at different loci.

11. Claims 1, 5, 54, 107, 253, 258, and 262 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aitman et al. '99 in view of Aitman et al. '97 as applied to claims 1-21, 23-25, 28-30, 33, 35-37, 40, 50, 52, 53, 252, 273, and 274 above, and further in view of Manly et al. (cited as reference C75 in the Information Disclosure Statement filed 06 March 2006, Mammalian Genome Vol. 10, pages 327-334 (1999))

The claims are drawn to a method of measuring an expression quantitative trait locus (eQTL), a clinical quantitative trait locus (cQTL), and determining whether the gene assayed in the determination of the eQTL and the clinical trait are associated by determining if the eQTL and cQTL map to the same locus. In some embodiments the claimed subject matter is a computer program or computer that executes the process. In some embodiments the mapping utilizes regression or interval mapping. In some embodiments the mapping utilizes a null hypothesis. In some embodiments the mapping utilizes a maximum likelihood analysis.

Aitman et al. '99 in view of Aitman et al. '97 as applied to claims 1-21, 23-25, 28-30, 33, 35-37, 40, 50, 52, 53, 252, 273, and 274 above discuss on page 82 the use of a computer program termed MAPMAKER, but Aitman et al. does not provide details of their genetic mapping calculations. Aitman et al. '99 in view of Aitman et al. '97 as applied to claims 1-21, 23-25, 28-30, 33, 35-37, 40, 50, 52, 53, 252, 273, and 274 above uses LOD statistical scoring at least in Aitman et al. '97 in Figure 1. The specification exemplifies use of the null hypothesis on page 69, lines 12-24 as inherent in use of LOD analysis.

Manly et al. reviews computer software for use in QTL analysis. Manly et al. shows in the second column of page 327 that two methods widely used are least squares regression and maximum likelihood estimation. Manly et al. also discusses use of interval mapping on pages 327-328 for use in QTL mapping. Manly et al. discusses use of LOD scores to determine a QTL in the first column of page 329. Manly et al. review a number of programs used for QTL mapping, including MAPMAKER (used by Aitman et al. '99 and Aitman et al. '97) on pages 329-330.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use a computer running the MAPMAKER program as shown in Aitman et al. because Manly et al. shows that MAPMAKER, as well as a number of other programs, are useful to map QTL markers. It would have been further obvious to use regression or maximum likelihood analysis, and additionally interval mapping and determining a LOD score because Manly et al. show that such analyses are useful to map QTL markers.

Response to Arguments

12. Applicant's arguments filed 12 November 2010 have been fully considered. New grounds of rejection have been raised in response to the amendment to the claims received 12 November 2010.

Allowable Subject Matter

13. Claims 259-261 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

14. A shortened statutory period for reply to this action is set to expire THREE MONTHS from the mailing date of this action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John S. Brusca/

Primary Examiner, Art Unit 1631

jsb